STATISTICAL ANALYSIS PLAN (SAP) FOR PROTOCOL CD1-NASH-01

Sponsor	CytoDyn, Inc. 1111 Main Street, Suite 660 Vancouver, Washington 98660
Protocol Number:	CDI-NASH-01
Protocol Title:	A Phase II, Multi-center, Two-Part (Part 1: Randomized, Double-Blind, Placebo-Controlled with Leronlimab 700mg and placebo; and Part 2: Open-label, Single Arm with Leronlimab 350mg), Three-Arm, Dose-Ranging Study of the Safety and Efficacy of Leronlimab (PRO 140) in Adult Patients with Nonalcoholic Steatohepatitis (NASH)
Clinical Protocol Version/Date:	Version 7 / 14-Jun-2021
SAP Author:	[redacted]
Approved by:	[redacted]

Confidentiality Statement

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GLOSSARY OF ABBREVIATIONS

AE	Adverse event
BMI	Body Mass Index
CAT	Categorical
CCR5	C-C chemokine receptor type 5
CI	Confidence Interval
CONT	Continuous
CRO	Clinical Research Organization
cT1	Corrected T1
eCRF	Electronic Case Report Form
EOT	End of treatment
ET	Early termination
FAS	Full Analysis Set
FU	Follow-Up
LTFU	Lost to follow-up
MRI	Magnetic Resonance Imaging
N	Number
NASH	Nonalcoholic steatohepatitis
PDFF	Proton Density Fat Fraction
PP	Per Protocol Set
PT	Preferred Term
SAP	Statistical Analysis Plan
SC	Subcutaneous
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event

1 INTRODUCTION

This Statistical Analysis Plan describes the planned analyses and reporting for the clinical trial protocol CDI-NASH-01 version 7.0 dated June 14, 2021 sponsored by CytoDyn Inc. The main objective of this plan is to provide details pertaining to statistical methodology, data conventions, and processes used for the analysis of data from this trial.

This Statistical Analysis Plan provides sufficient detail to meet the regulatory and statistical profesional guidelines [1-6].

2 PROTOCOL DESIGN AND OBJECTIVES

2.1 Study Objectives

Primary Objective:

- The Primary objective of this study is to assess the efficacy of Leronlimab (PRO 140) in improving liver function in adult patients diagnosed with NASH compared to placebo

Secondary Objective:

- The Secondary objective of this study is to assess the safety and tolerability of Leronlimab (PRO 140) in adult patients diagnosed with NASH compared to placebo

2.2 Study Design

This is a phase II, multi-center, two-part study.

- Part 1. Randomized, double-blind, placebo-controlled, two-arm with 60 patients designed to evaluate the safety, tolerability, and efficacy of leronlimab (PRO 140 700mg dose) or placebo weekly administered subcutaneously (SC) in patients with NASH for 13 weeks.
- Part 2. Non-randomized, single-arm, open-label with 30 patients designed to evaluate the safety, tolerability, and efficacy of leronlimab (PRO 140 350mg dose) weekly administered subcutaneously (SC) in patients with NASH for 13 weeks SC in patients with NASH for 13 weeks

For Part 1 of the study leronlimab 700mg group will be compared to placebo.
For Part 2 of the study leronlimab 350mg group will be compared to placebo from Part 1.

The study schematic is presented in Figure 2.1 and Figure 2.2

Figure 2.1: Study Schematic

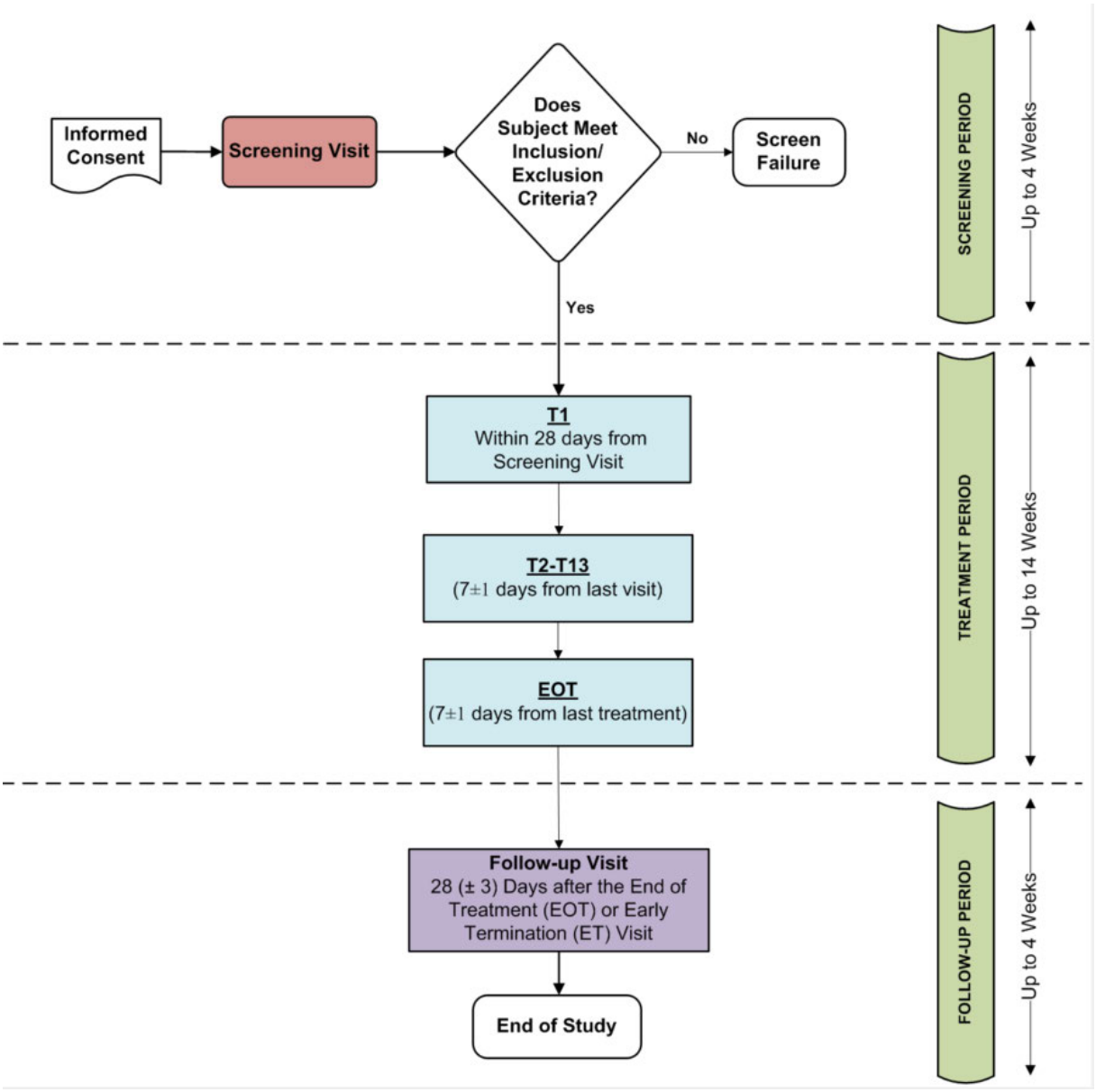
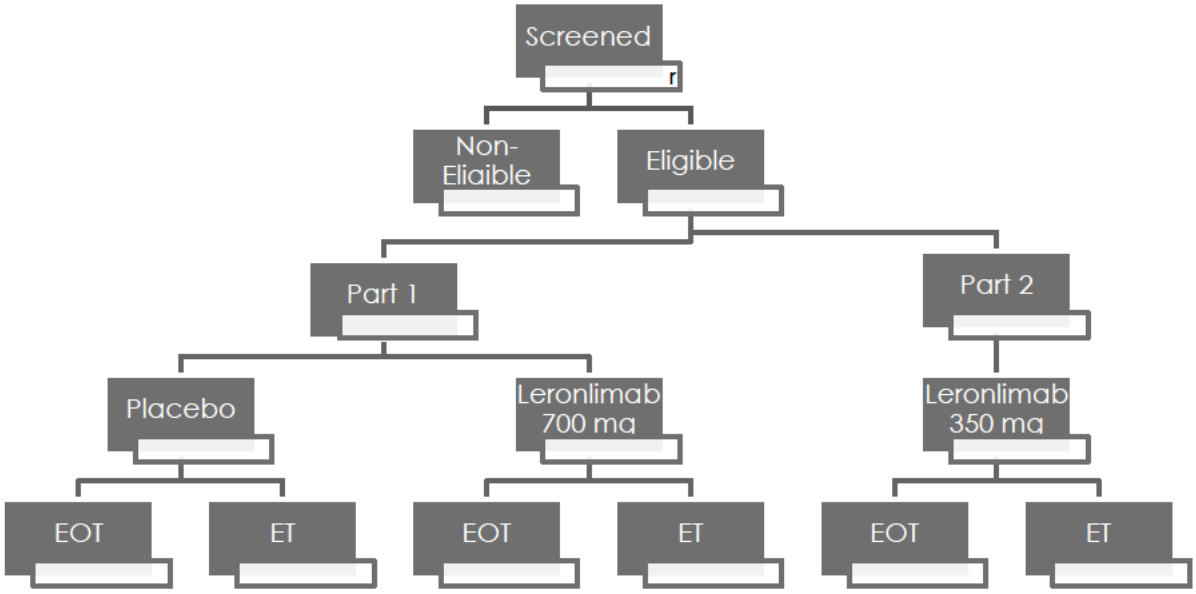


Figure 2.2



See Section 3.3 in the protocol for eligibility and exclusion.

Subjects who complete the treatment period will continue to End of Treatment (EOT) Visit assessments at week 14 and enter the Follow-up Phase of the study. Subjects who meet any criteria for discontinuation of study treatment as specified in Section 5.1 of the protocol, will undergo Early Termination (ET) Visit assessments 7 days after the last injection and enter the Follow-up Phase of the study.

A Follow-up visit will be conducted 28 (± 3) days after the End of Treatment (EOT) or Early Termination (ET) Visit.

See Table 4-2 of the protocol for detailed study schedule.

2.3 Study Duration

The total Study Duration is up to 22 weeks:

- Screening Period: Up to 4 weeks
- Treatment Period: Up to 14 weeks
- Follow-Up Period: Up to 4 weeks after End of Treatment (EOT) or Early Termination (ET) Visit

2.4 Study Centers

Up to 20 centers in the United States (US).

2.5 Study Target Population

Adult patients with NASH who meet the eligibility criteria will be enrolled.

2.6 Study Treatments

In Part 1 of study leronlimab 700mg or placebo will be subcutaneously administered every week by a licensed healthcare professional at the study site for 13 weeks.

Part 1
Treatment Groups

STUDY DRUG	DOSE	ROUTE	SCHEDULE
Leronlimab	700mg	SC	Start on Day 1 and every week thereafter
Placebo	N/A	SC	Start on Day 1 and every week thereafter

In Part 2 of the study, the non-randomized, single-arm, open-label phase, leronlimab 350mg dose) will be administered subcutaneously (SC) weekly for 13 weeks.

Part 2
Treatment Groups

STUDY DRUG	DOSE	ROUTE	SCHEDULE
Leronlimab	350 mg	SC	Start on Day 1 and every week thereafter

2.7 Randomization

Part 1:

Subjects who are eligible to participate in the trial will be randomized 1:1 to one of the treatment groups via IWRS (Interactive Web Based Randomization System) at the Visit prior to IP administration. The randomization will be central and will use 1:1 ratio of Treatment groups

- Leronlimab 700mg SC weekly injection
- Placebo 0mg SC weekly injection

Part 2:

Randomization is not applicable for the open-label, single-arm portion (Part 2) of the study.

2.8 Blinding

All subjects, investigators and their staff, and all Sponsor/CRO personnel involved in the management of the study will be blinded to treatment assignments.

Treatment unblinding for the study will occur after all clinical data have been received, data inconsistencies have been resolved, and the database is locked, except for safety reasons on a case-by-case basis (i.e., emergency unblinding).

Note: Blinding is not applicable for the open-label, single-arm portion (Part 2) of the study.

2.9 Protocol Deviations

The protocol deviations will be classified as minor and major deviations before unblinding.

2.9.1 Major Protocol Deviations

The following deviations will be considered as major protocol deviation: and will result in exclusion from PP analysis set:

- Dietary noncompliance clinically significant as deemed per investigator
- Noncompliance with amount of alcohol use as stipulated in exclusion criteria during the study
- Poor diabetic control with consistent elevated fasting blood glucose >=200
- Noncompliance with diabetic and or lipid lowering medications clinically significant as deemed per investigator
- Use of Hepatotoxic medications clinically significant as deemed per investigator: including but not limited to: Isoniazid, glucocorticoids- prednisone, NSAIDS, Paracetamol, Ketoconazole, Hydralazine, Iproniazid.
- Missing 2 consecutive doses of IP or less than 80% cumulative compliance
- Not meeting inclusion or exclusion criteria
- Early termination before 14-week evaluation period
- T1 labs meeting exclusion criteria including but not limited to HbA1C >9, abnormal TSH and panel, autoimmune disorder with associated hepatitis. Elevations of CRP at T1 should be considered as potential autoimmune etiology until proven otherwise if workup was not performed prior to screening.

3 STUDY ENDPOINTS

3.1 Primary Endpoint

The primary endpoint for Part 1 of the study is:

Change from baseline in hepatic fat fraction assessed by magnetic resonance imaging-derived proton density fat fraction (MRI-PDFF) at week 14.

3.2 Secondary Endpoints

The secondary endpoints for Part 1 of the study are

- Change from baseline in fibro-inflammatory activity as assessed by cT1 (corrected T1) assessed by multiparametric magnetic resonance imaging (MRI) of liver at week 14 (Note: cT1 measured in milliseconds is a quantitative metric for assessing a composite of liver inflammation and fibrosis) fibrosis).
- Change from baseline in liver fibrosis using FibroTest at week 14
- Change from baseline in hepatic inflammatory activity using FibroTest at week 14
- Change from baseline in serum pro-inflammatory biomarkers assessments
- Change from baseline in Gamma-glutamyltransferase (GGT) at week 14
- Change from baseline in Cytokeratin 18 (CK-18) level at week 14
- Change from baseline in Leronlimab (PRO 140) PK assessments

The secondary endpoints for Part 2 of the study are:

- Change from baseline in fibro-inflammatory activity as assessed by cT1 (corrected T1) assessed by multiparametric magnetic resonance imaging (MRI) of liver at week 14 (Note: cT1 measured in milliseconds is a quantitative metric for assessing a composite of liver inflammation and fibrosis) compared to part 1 placebo
- Change from baseline in liver fibrosis using FibroTest at week 14 compared to Part 1 placebo
- Change from baseline in hepatic inflammatory activity using FibroTest at week 14 compared to Part 1 placebo
- Change from baseline in serum pro-inflammatory biomarkers assessments compared to Part 1 placebo
- Change from baseline in Gamma-glutamyltransferase (GGT) at week 14 compared to Part 1 placebo
- Change from baseline in Cytokeratin 18 (CK-18) level at week 14 compared to Part 1 placebo
- Change from baseline in Leronlimab (PRO 140) PK assessments compared to Part 1 placebo

3.3 Exploratory Endpoints

The exploratory endpoints for Part 1 of the study are

- The fibrosis scores categorized by degree of liver fibrosis as per cT1 value:
    - Mild 800-850 cT1
    - Moderate 851-999 cT1
    - Mild-Moderate 800-999 cT1
    - Severe >=1000 cT1
- Change from baseline in Alanine transaminase (ALT) at week 14
- Change from baseline in Aspartate transaminase (AST) at week 14
- Change from baseline in total bilirubin at week 14
- Change from baseline in triglycerides at week 14
- Change from baseline in Low Density Lipoprotein (LDL) at week 14
- Change from baseline in High Density Lipoprotein (HDL) at week 14
- To explore Monocyte/T cell CCR5 biomarkers that may predict activity of leronlimab.

3.4 Safety Endpoints

Safety endpoints of the study are:

- Adverse events (AEs)
- Laboratory parameters (blood tests, urinalysis)
- Vital signs (blood pressure, heart rate)
- Subject's medical condition (physical examination including weight)
- Tolerability of repeated subcutaneous administration of Leronlimab (PRO 140) will assessed by
    - Subject rated 11-point Numeric Pain Rating Scale
    - Investigator-evaluation of injection site reactions.

4 SAMPLE SIZE

The sample size of 90 total subjects [60 subjects (30 subjects per arm) for the Randomized Phase and up to 30 subjects for the non-randomized, open-label phase] is based on clinical judgment. The number of subjects is deemed adequate to provide clinically meaningful descriptive results consistent with study objectives.

5 INTERIM ANALYSIS

No interim analysis (IA) will be performed.

6 PRIMARY HYPOTHESIS TO BE TESTED

The null hypothesis of no between treatment group difference in mean change from baseline to Week 14 in Proton Density Fat Fraction (MRI-PDFF) will be tested against the alternate hypothesis of a non-zero difference.

7 ANALYSIS SETS

7.1 Full Analysis Set

Full anaysis set (FAS) will be the set of subjects which is as complete as possible and as close as possible to the intention-to-treat ideal of including all randomized subjects. The FAS is defined as the set of subjects who

- Receive at least one dose of study treatment
- Have at least one post-baseline efficacy assessment
- Subjects who fail to satisfy an entry criterion may be excluded from FAS only under the following circumstances: The entry criterion was measured prior to randomization, the detection of the relevant eligibility violations was made completely objectively, all subjects receive equal scrutiny for eligibility violations and all detected violations of the particular entry criterion are excluded.

The FAS will be used as the primary analysis set.

The randomized treatment will be used for primary efficacy analysis.

7.2 Per Protocol Set

The PP set will be used as the supportive analysis set.

The Per Protocol (PP) population is defined as the set of subjects who meet the intention to treat requirements, were not associated with any major protocol violations and have at least 80% compliance with study treatment. This population will be identified before the database lock.

Per protocol set (PP) will be subset of the subjects in the full analysis set who were not associated with any major protocol violations and have at least 80% compliance with study

treatment. Subjects will be excluded from the PP if a major protocol deviation occurred. The criteria for major protocol deviations are listed in Section entitled Protocol Deviations.

The actual treatment will be used for the Per Protocol efficacy analysis.

7.3 Safety Analysis Set

The Safety Analysis set will comprise all subjects who have received one dose of study treatment. This analysis set will be used for the analysis of safety variables.

Actual treatment received will be used for safety analysis in event of a major protocol deviation.

8 DATA HANDLING CONVENTIONS

8.1.1 Data entry errors and potential outliers

Patients may have potential outliers for particular observations. Potential outliers based on correct values will be included in the analysis. However, sensitivity analyses excluding outliers may be calculated to evaluate the influence of such extreme values. Values found to be incorrect due to data entry error will be excluded from all analyses as missing values. Incidence of incorrect values and potential outliers may be listed and summarized per treatment arm. If assumptions or data structure do not allow planned analyses, analyses will be updated appropriately.

8.1.2 Missing data

Subjects may have missing specific data points for a variety of causes. In general, data may be missing due to a missed visit, non-evaluability of a specific clinical measurement at its planned clinical visit or a subject's early withdrawal from study. All data will be used as observed, and no imputations will be made for any missing data point.

8.1.3 Partial dates

Partially incomplete dates will be imputed for dates related to events and follow up information. Dates with missing months or years will not be imputed. Derived data from these dates will be calculated using only the information that is available.

Imputation will be done as described in the following table:

	MISSING	IMPUTE	DURATION CALCULATION
Date	Day	15	Duration will be presented in days and is calculated as the difference between date1 and date2
Date	Month	NONE	Duration will be presented in years and is calculated as the difference between year1 and year2. Example: Duration of NASH diagnosis

8.1.4 Derived data

BMI : Body Mass Index is the weight in kilograms divided by the square of height in meters

BMI category: Based upon the calculated value of BMI, patients will be categorized into the subcategories

- Underweight : <18.5
- Healthy weight : 18.5 – 24.9
- Overweight : 25.0 – 29.9
- Low risk obesity : 30.0 – 34.9
- Moderate risk obesity : 35.0 – 39.9
- High risk obesity : >=40.0

Heart rate: the measurements will be categorized as

- Slow: <60 beats per minute
- Normal : 60-100 beats per minute
- Fast :>100 beats per minute

Blood pressure: To evaluate blood pressure results of systolic and diastolic measurements are combined to denote hypertension

- Hypertension: Systolic>=140 and Diastolic>=90
- No hypertension : All other combinations

Duration of NASH diagnosis: Time period in years between date of initial NASH diagnosis and randomization date in the study

Grade change from baseline to week 14 in CT1 by degree of fibrosis

- In patients with CT1 800-849 msec mild
- In patients with CT1 850-999 msec moderate
- In patients with CT1 ≥ 1000 msec severe

End of Treatment (EOT): Subjects who complete the treatment period of 13 weeks have reached their End of Treatment.

Early Termination (ET): Subjects who meet any criteria for discontinuation of study treatment, as specified in Section 5.1 of the protocol, will undergo Early Termination (ET).

Medications:

- Concomitant medications will be coded using WHO dictionary and associated with ATC levels 1 and 2:

Adverse Events:

- Treatment Emergent AE’s (TEAE) are defined as events with an onset on or after the first treatment.

- System Organ Class (SOC) and preferred terms (PT) will be associated with each adverse event using most recent version of Medical Dictionary for Regulatory Activities (MedDRA).

8.1.5 Analysis Data for Regulatory Submission

Data collected during this study as well as the derived data will be formatted to meet the SDTM (Study Data Tabulation Model) and the Analysis Data Model (ADaM) standards of Clinical Data Interchange Standards Consortium (CDISC). A standard Define.doc file that describes the data attributes will be provided,

9 STATISTICAL METHODS

9.1 GENERAL STATISTICAL CONSIDERATIONS

All statistical summaries and analyses will be performed using SAS® for Windows, version 9.4 or later.

Collected study data will be presented in subject data listings.

For continuous variables descriptive statistics (n, mean, standard deviation, median, minimum and maximum) will be presented by treatment group.

For categorical variables data summaries by treatment group will include frequency counts and percentages.

Formal treatment group comparisons will be made at the nominal two-sided 0.05 level of significance using the FAS and PP analysis sets. The 95% confidence intervals and p-values for comparing treatment groups will be computed.

9.1.1 Mock Table Shells

A separate document will be created that describes the format of the statistical Listings and Tables (i.e. mock table shells)

9.1.2 Covariates

For efficacy analyses the baseline values will be used as a covariate.

9.1.3 Protocol Deviations

Subject listing of major protocol deviations by treatment group will be provided.

9.1.4 Analysis sets

The number of subjects in each analysis set will be computed for each part of the study and treatment group and overall.

Number of Subjects in Analysis Set

	PART 1		PART 2	
	PLACEBO	LERONLIMAB 700 MG	OVERALL	LERONLIMAB 350 MG
Full Analysis set (FAS)	n	n	n	n
Per protocol set (PP)	n	n	n	n
Safety analysis set	n	n	n	n

9.1.5 Subject Disposition and Withdrawals

The disposition of all subjects who sign an ICF will be provided. The numbers of subjects screened, randomized, received treatment, completed study, terminated early, and reasons fortermination will be listed and/or summarized by treatment group.

Summary of Subject Disposition

	PART 1		PART 2
	PLACEBO N (%)	LERONLIMAB 700 MG N (%)	LERONLIMAB 350 MG N (%)
Assessed for screening	n (xx)	n (xx)	n (xx)
Eligible at screening	n (xx)	n (xx)	n (xx)
Ineligible at screening	n (xx)	n (xx)	n (xx)
Eligible and randomised	n (xx)	n (xx)	n (xx)
Received randomized therapy	n (xx)	n (xx)	n (xx)
Not received randomized therapy	n (xx)	n (xx)	n (xx)
End of Treatment	n (xx)	n (xx)	n (xx)
Early Termination	n (xx)	n (xx)	n (xx)
ET – LTFU	n (xx)	n (xx)	n (xx)
ET- PATIENT WISH	n (xx)	n (xx)	n (xx)
ET – AE	n (xx)	n (xx)	n (xx)
ET - Other	n (xx)	n (xx)	n (xx)

9.1.6 Demographic and Baseline Disease Characteristics

Demographics and baseline disease characteristics medical history, prior and concomitant medications/therapies will be summarized by treatment group

The following variables will be summarized descriptively using frequency counts and/or summary statistics n, mean, sd, median, min and max, as appropriate:

VARIABLE	TYPE	PRESENTATION
Age	CONT	In years
Gender	CAT	Male vs Female
Racial categories	CAT	Non-Hispanic Caucasian Hispanic Black/African American Asian Natives Other

BMI	CONT	Continuous
BMI category	CAT	Underweight : <18.5 Healthy weight : 18.5 – 24.9 Overweight : 25.0 – 29.9 Low risk obesity : 30.0 – 34.9 Moderate risk obesity : 35.0 – 39.9 High risk obesity : >=40.0
Blood pressure	CAT	Hypertension: Systolic>=140 and Diastolic>=90 No hypertension : All other combinations
Heart rate	CAT	Slow : <60 beats per minute Normal : 60-100 beats per minute Fast :>100 beats per minute
Alcohol consumption	CAT	Never/Current/Former
Duration NASH diagnosis	CONT	Duration in years
Nash medication	CAT	None/unknown/yes
Stage Liver Fibrosis histology	CAT	F0/F1/F2/F3/F4/Unknown
Stage Steatosis histology	CAT	S0/S1/S2/S3
Stage Steatosis CAP US	CAT	S1 238-260 S2 260-290 S3 >290
Stage Fibrosis US	CAT	F0-F1 2-7 F2 7.5 -10 F3 10 – 14 F4 >14
cT1	CONT	
PDFF	CONT	
Co-morbidities	CAT	Yes/No
Number of co-morbidities	CAT	0-5 5-10 10-15 15-20 20-25 >25
Concomitant medication	CAT	Yes/No
Number of concomitant medications	CAT	0-5 5-10 >10

9.1.7 Alcohol Consumption and Related Variables

For the patient population entering the study alcohol consumption variables will be summarized as follows:

Summary of Alcohol Consumption and Related Variables

	PART 1	PART 2

ALCOHOL CONSUMPTION	PLACEBO (N=NN)	LERONLIMAB 700 MG (N=NN)	LERONLIMAB 350 MG (N=NN)
Never	n (xx%)	n (xx%)	n (xx%)
Current	n (xx%)	n (xx%)	n (xx%)
Former	n (xx%)	n (xx%)	n (xx%)

9.1.8 Medical History

Medical history of the subjects will be listed and summarized by treatment group.

Summary of Medical History
N (%)

	PART 1		PART 2
	PLACEBO (N=NN)	LERONLIMAB 700 MG (N=NN)	LERONLIMAB 350 MG (N=NN)
	n (xx%)	n (xx%)	n (xx%)
	n (xx%)	n (xx%)	n (xx%)
	n (xx%)	n (xx%)	n (xx%)

9.1.9 Concomitant Medications

Concomitant medications will be coded using WHO dictionary. Concomitant medications will be listed and summarized by treatment group and ATC levels 1 and 2:

Concomitant Medications
N (%)

	PART 1		PART 2
	PLACEBO (N=NN)	LERONLIMAB 700 MG (N=NN)	LERONLIMAB 350 MG (N=NN)
Anatomic Group			
Therapeutic subgroup			
Preferred Drug Name			
Alimentary Tract and Metabolism			
Drugs For Acid Related Disorders			
OMEPRAZOLE	n (xx)	n (xx)	n (xx)
RANITIDINE	n (xx)	n (xx)	n (xx)

9.2 Analysis of efficacy data

Data for each part of the study will be analysed separately. For Part 1 of the study leronlimab 700mg group will be compared to placebo. For Part 2 of the study leronlimab 350mg group will be compared to placebo from Part 1.

9.2.1 Analysis of Primary Efficacy Endpoint

The null hypothesis of no between treatment group difference in mean change from baseline in hepatic fat fraction assessed by magnetic resonance imaging-derived proton density fat fraction (MRI-PDFF) at week 14 against alternate hypothesis of a non-zero treatment-difference will be tested at 0.05 level of significance.

A preliminary assessment of normality will be performed using Shapiro-Wilks test at the 5% significance level.

If departure from normality is not concluded a normality-based parametric test of the null hypothesis will be performed using ANCOVA with baseline as a continuous covariate and treatment group as a categorical covariate. The point estimate of the mean (SD) along with corresponding 95% confidence interval will be presented. The baseline adjusted estimates of the treatment means and treatment difference along with 95% confidence interval and the two-sided p-values will be presented.

Otherwise, the null hpothsis will be tested using the two-sample Wilcoxon Rank Sum test and the Hodges-Lehmann estimate of location shift along with the corresponding 95% confidence intervals will be reported.

Even if the parametric analysis is deemed appropriate, the non-parametric analyses will be performed to assess the robustness of the conclusions based on ANCOVA.

Summary of MRI-PDFF
Method: ANCOVA

	PART 1			
	PLACEBO (N=NN)	LERONLIMAB 700MG (N=NN)	DIFFERENCE 95%CI (Lower-Upper)	P-VALUE [1]
Number. of Subjects	nn	nn		
Baseline	xx.x (xx.x)	xx.x (xx.x)		
Week 14	xx.x (xx.x)	xx.x (xx.x)		
Change at WK14	xx.x (xx.x)	xx.x (xx.x)		
Baseline Adjusted Change at WK14	xx.x (xx.x)	xx.x (xx.x)	xx.xxx (xx.x) (xx.xxx-xx.xxx)	0.xxx

[1] p-value computed using ANCOVA accounting for treatment and baseline as covariates.

**Programming note1: Create similar tables for Method=Non-parametric, change headers and footers accordingly.*
**Programminmg note 2: Repeat these tables for Part 2.*

9.2.2 Analysis of Secondary Endpoints

The secondary efficacy endpoints will be analyzed as follows:

Analysis of Change from Baseline in Fibro-Inflammatory Activity

Change from baseline in fibro-inflammatory activity as assessed by cT1 (corrected T1) assessed by multiparametric magnetic resonance imaging (MRI) of liver at week 14 will be summarized. The secondary endpoints including change from baseline in cT1, will be assessed in a manner like the assessment of the primary endpoint.

Analysis of Fibro-Inflammatory Activity Categories

Frequencies will be computed for cT1 grade categories (Mild: 1 ≥ 800-850) Moderate: (851-999, Severe: (≥ 1000) and treatment. The treatment groups will be compared using Cochran-Mantel Haenszel chi-square (CMH) test.

Summary of Fibro-Inflammatory Activity Grades Based on cT1 Scores
n (%)

	PART 1*		
	PLACEBO (N=XX)	LERONLIMAB 700 MG (N=XX)	P-VALUE [1]
Mild (1 ≥ 800-850)	n (xx)	n (xx)	
Moderate (851-999)	n (xx)	n (xx)	0.xxx
Severe (≥ 1000)	n (xx)	n (xx)	

[1] p-value computed using CMH chi-square test.

**Programming note: Repeat summary table for Part 2*

Analysis of Other Continuous Secondary Endpoints

Change from baseline to Week 14 in the continuous secondary endpoints will be analyzed using methods like the one used for the primary endpoint.

- liver fibrosis using FibroTest at week 14
- hepatic inflammatory activity using FibroTest at week 14
- serum pro-inflammatory biomarkers assessments
- Gamma-glutamyltransferase (GGT) at week 14
- Cytokeratin 18 (CK-18) level at week 14
- Leronlimab (PRO 140) PK assessments

9.2.3 Analysis of Exploratory Outcome Measures

The exploratory efficacy endpoints are:

Alanine transaminase (ALT) at week 14
Aspartate transaminase (AST) at week 14
Total bilirubin at week 14
Triglycerides at week 14

Density Lipoprotein (LDL) at week 14

Analysis of Continouos Exploratory Endpoints

Change from baseline to Week 14 in the continuous exploratory endpoints will be analyzed using methods like the one used for the primary endpoint.

9.2.4 Analysis of CCR5 Biomarkers that may Predict Activity of Leronlimab

To examine if monocyte/T cell CCR5 biomarker is predictive of leronlimab activity, the statistical significance of biomarker and treatment group interaction group will be assessed. The change from baseline to Week 14 in MRI-PDFF (and cT1) will be regressed on biomarker and treatment group and their interaction as covariables. The p-values for these effects will be presented:

Summary of Biomarker as a Predictive Factor
PART 1*

	p-value		
**	Bio-marker	Treat-ment	Inter-action
Pro-inflammatory Biomarkers	0.xxx	0.xxx	0.xxx
IL-1 alpha	0.xxx	0.xxx	0.xxx
IL-1 beta	0.xxx	0.xxx	0.xxx
IL-6	0.xxx	0.xxx	0.xxx
RANTES (CCL5)	0.xxx	0.xxx	0.xxx
TNF-alpha	0.xxx	0.xxx	0.xxx
TNF-beta	0.xxx	0.xxx	0.xxx
CRP	0.xxx	0.xxx	0.xxx
Fibro Test			
Gamma-glutamyltransferase	0.xxx	0.xxx	0.xxx
Total bilirubin	0.xxx	0.xxx	0.xxx
Alpha-2-macroglobulin	0.xxx	0.xxx	0.xxx
Apolipoprotein A1	0.xxx	0.xxx	0.xxx
Haptoglobin.	0.xxx	0.xxx	0.xxx
ALT	0.xxx	0.xxx	0.xxx
Liver Function Tests / NASH Markers	0.xxx	0.xxx	0.xxx
Total Bilirubin	0.xxx	0.xxx	0.xxx
Direct Bilirubin	0.xxx	0.xxx	0.xxx
Alkaline Phosphatase (ALP)	0.xxx	0.xxx	0.xxx
Alanine Aminotransferase (ALT) (or SGPT)	0.xxx	0.xxx	0.xxx
Aspartate Aminotransferase (AST) (or SGOT)	0.xxx	0.xxx	0.xxx
Prothrombin Time (PT)	0.xxx	0.xxx	0.xxx
International Normalized Ratio (INR)	0.xxx	0.xxx	0.xxx
Albumin	0.xxx	0.xxx	0.xxx
Total Protein	0.xxx	0.xxx	0.xxx
Triglycerides	0.xxx	0.xxx	0.xxx
Cholesterol (Low density lipoprotein)	0.xxx	0.xxx	0.xxx
Cholesterol (High density lipoprotein)	0.xxx	0.xxx	0.xxx

Creatine kinase	0.xxx	0.xxx	0.xxx
Gamma-glutamyltransferase (GGT)	0.xxx	0.xxx	0.xxx
Serum CK-18	0.xxx	0.xxx	0.xxx

**Programming Note 1: Repeat for Part 2 using Plaebo from Part 1 in the statistical model*

***Programming Note2: Please adjust the list according to the actual lab data.*

9.3 Analysis of Safety Data

9.3.1 Extent of Exposure

The duration of exposure will be categorized as 0-2 weeks,2-4 weeks, 4-8 weeks, 8-12 weeks, and >12 weeks. Actual categories will be specified at the time of reporting to adequately summarize the extent of exposure. The number and percentage of subjects in each category will be summarized using number (%) of subjects by treatment group and category.

Summary of Extent of Exposure
N (%)

DURATION (WEEKS)	PLACEBO	LERONLIMAB 700MG	LERONLIMAB 350MG
	xx (xx%)	xx (xx%)	xx (xx%)
0-2	xx (xx%)	xx (xx%)	xx (xx%)
2-4	xx (xx%)	xx (xx%)	xx (xx%)
4-8	xx (xx%)	xx (xx%)	xx (xx%)
8-12	xx (xx%)	xx (xx%)	xx (xx%)
>12	xx (xx%)	xx (xx%)	xx (xx%)
	xx (xx%)	xx (xx%)	xx (xx%)

9.3.2 Adverse Events

Since in each part of this study, surveillance of adverse events (AE) will begin from the time the subject receives study treatment until the end of the study, all AEs in this study are considered treatment-emergent AEs (TEAEs). The TEAEs verbatim text recorded in the data base will be coded to associate MedDRA System Organ Classes (SOCs) and preferred term (PT).

TEAEs will be listed and summarized as follows.

Listing of Subject Numbers for Adverse Events

SYSTEM ORGAN CLASS Preferred Term	TREATMENT	NO. WITH EVENT	SUBJECT NUMBERS
SOC1			
Preferred term a	Placebo	3	xxx, xxx, xxx
	Leronlimab 700 mg	2	xxx, xxx

	Leronlimab 350 mg	1	xxx
Preferred term b	Placebo	3	xxx, xxx, xxx
	Leronlimab 700 mg	2	xxx, xxx
	Leronlimab 350 mg	1	xxx

Listing of Relationship of Adverse Event SOCs, and Verbatim Text

SYSTEM ORGAN CLASS	PREFFERED TERM	VERBATIM TEXT
SOC1	xxxxxx xxxxxxx xxxxxx xxxx	xxxxxxx xxxxxx xxxxxxxxx
SOC 2	xxxxxx xxxxxxx xxxxxx xxxx xxxxxx	xxxxxxx xxxxxx xxxxxxxxx xxxxxxx

Adverse Event Subject Listings

Subject listings of adverse events will be sorted by treatment, subject number, SOC and PT will be provided and will display the following variables:

- Treatment group
- Subject Number
- System Organ Class (SOC)
- Preferred Term (PT)
- CTCAE Intensity Grade Assessment (1-5)
- Relationship to study treatment (Causality: Unrelated, Unlikely, Possibly, probably, Definitely)
- Treatment given to treat the event
- Outcome (fatal, not recovered/not resolved, recovered/resolved, recovered/resolved with sequalae, recovering/resolving, and unknown),
- Seriousness (Y/N)
- Impact (dose increased, dose not changed, dose reduced, drug interrupted, drug withdrawn, unknown, and not applicable)

Following subject listings will be produced:

- Subject listing of all adverse events
- Subject listing of fatal adverse events
- Subject llisting of non-fatal adverse events
- Subject listing of adverse events of special interest (injection site reaction)
- Subject listing of serious adverse events
- Subject listing of adverse events leading to withdrawal

Subject Listing of All Adverse Events*

Treatment: Placebo*

Subject	Age Sex Race Weight	Preferred term/ Verbatim text	Outcome/ Onset date/ Resolution date	Time since 1st dose/ Time since last dose	Intensity/ Seriousness/ Withdrawal	Action taken/ Relationship to Study drug
xxx	xxxx/ xxx/ xxxx/ xxxx	xxxxxxxxx/ xxxxxxxxx	xxx/ xxx/ xxxxx	xxxxx xxxxx	xxxxx/ xxxx/ xxxx	xxxxx/ xxxxxxx
xxx	xxxx/ xxx/ xxxx/ xxxx	xxxxxxxxx/ xxxxxxxxx	xxx/ xxx/ xxxxx	xxxxx xxxxx	xxxxx/ xxxx/ xxxx	xxxxx/ xxxxxxx

**Programming note: Repeat for fatal, non-fatal, events of special interest, serious and adverse events leading to withdrawal*

Adverse Event Summaries

For the purposes of summarizing the TEAEs, the adverse event summaries will be sorted by MedDRA System Organ Classes (SOCs), in descending order from the SOC with the highest total incidence (i.e., summed across all treatment groups) for any adverse event within the class to the SOC with the lowest total incidence. Within each level, adverse events will be presented in descending order from the adverse event with the highest total incidence to the lowest total incidence. If the total incidence for any two or more adverse events is equal, the events will be presented in alphabetical order. Levels will not be presented if no adverse events occur within the level.

The following TEAE summaries will be provided:

- Summary of all adverse events
- Summary of drug-related adverse events
- Summary of serious adverse events
- Summary of adverse events leading to withdrawal

Summary of All Adverse Events*

	PART 1 PLACEBO (N=X)	PART 1 LERONLIMAB 700 MG (N=XX)	PART 2 LERONLIMAB 350MG (N=XX)
ANY EVENT	n (xx%)	n (xx%)	n (xx%)
SOC	n (xx%)	n (xx%)	n (xx%)
Any event	n (xx%)	n (xx%)	n (xx%)
PT 1	n (xx%)	n (xx%)	n (xx%)
PT 2	n (xx%)	n (xx%)	n (xx%)

**Programming note: Repeat for drug-related, serious and events leading to withdrawal.*

9.3.3 Clinical Laboratory Assessments

All laboratory values Including Height, Weight and BMI will be listed. These variables will also be summarized as continuous variable and presented by treatment group and time point. For the purpose of this study, the below baseline (normal) values/reference range for the liver function panel be flagged:

Total Bilirubin	0.2-0.9 mg/dl
Direct Bilirubin	0.0 – 0.2 mg/dl
SGOT (AST)	15-41 IU/L
SGPT (ALT)	M: 17-63 IU/L; F: 14-54 IU/L
Alkaline Phosphatase (ALP)	34-104 IU/L

Subject listing of Clinical Laboratory Data:

Part 1, Treatment: Placebo

Subject	Age Sex Race Weight	Lab test (Units)	Visit	Value	Normal range	Flag
xxx						

Normal range flag: H=above range, L=below range.

Subject Listing of Height, Weight, and BMI

	Treat-ment	Investi-gator	Subject	Visit	Height	Weight	BMI
Part 1	Placebo Leronlimab 700 mg						
Part 2	Leronlimab 350 mg						

The clinical laboratories at every assessed time point and changes from baseline will be summarised using the minimum set of summary statistics n, mean, SD, Median, Min and Max

Summary of Laboratory Data

Laboratory: xxxxx*

	Treatment	N	Visit	n	Mean	SD	Median	Min	Max
Part 1	Placebo Leronlimab 700 mg								

Part 2	Leronlimab 350 mg

**Programming note: Repeat for all labs*

9.3.4 Physical Examination

Subject-listing of abnormalities noted during physical examination including Weight will be presented.

Listing of Abnormalities in Physical Examination

	TREAT-MENT	INVESTI-GATOR	SUBJECT	VISIT	ABNORMALITY
Part 1	Placebo				
	Leronlimab 700 mg				
Part 2	Leronlimab 350 mg				

9.3.5 Vital Signs

Subject-listing of vital signs will be presented.

Subject Listing of Vital Signs

	Treatment	Inv.	Subj.	Age(y)/ Sex/ Race	Visit	Systolic BP (mmHg)	Diastolic BP (mmHg)	Vital Sign 3 (units)
Part 1	Placebo	xx	xx	23/	xx	xx H	xx L	x H
				Male/	xx	xx	xx	xx H
				White	xx	xx	xx H	xx

The vital signs at every assessed time point and changes from baseline will be summarised using the minimum set of summary statistics n, mean, SD, Median, min and max.

Summary of Systolic BP (mmHg)*

	Treatment	N	Visit	n	Mean	SD	Median	Min	Max
Part 1	Placebo								
	Leronlimab 700 mg								
Part 2	Leronlimab 350 mg								

**Programming note: Repeat for Diastolic BP (mmHG) and Heart Rate*

9.3.6 Electrocardiogram (ECG)

Ventricular rate (beats per minute), PR interval (msec), QRS interval (msec), QT interval (msec), and QTc interval (msec). Additionally, the Investigator will record the overall results of the ECG reading as either normal or abnormal, and as either not clinically significant or clinically significant. If abnormalities are observed, each will be recorded. Subject-listing of ECG values will be presented.

The ECG at each assessed time point and changes from baseline will be summarised using the minimum set of summary statistics n, mean, SD, Median, Minimum and maximum

Summary of Ventricular rate (beats per minute)

	Treatment	N	Visit	n	Mean	SD	Median	Min	Max
Part 1	Placebo								
	Leronlimab 700 mg								
Part 2	Leronlimab 350 mg								

**Programming note: Repeat for PR interval (msec) QRS interval (msec), QT interval (msec), and QTc interval (msec).*

Summary of Overall Result of 12-Lead ECG

	TREAT-MENT	VISIT	NORMAL	ABNORMAL	CLINICALLY NOT SIGNIFICANT	CLINICALLY SIGNIFICANT
Part 1	Placebo	xx	xx (xx)	xx (xx)	xx (xx)	xx (xx)
	Leronlimab 700 mg	xx	xx (xx)	xx (xx)	xx (xx)	xx (xx)
Part 2	Leronlimab 350 mg	xx	xx (xx)	xx (xx)	xx (xx)	xx (xx)

9.3.7 Tolerability

Tolerability of repeated injections will be assessed by

- Subject rated 11-point Numeric Pain Rating Scale (0=None to 10=Worse)
- Investigator-evaluation of injection site reactions

Subject Injection Site Pain Rating Score

A subject lising of pain score will be presented.

The frequencies of subject rated pain score will be computed

Summary of Inject Site Pain Score
N (%)

	Placebo (N=nn)	Leronlimab 700 mg (N=nn)	Leronlimab 350 mg (N=nn)
Severity[1]			
0-5	xx (%)	xx (%)	xx (%)
6-7	xx (%)	xx (%)	xx (%)
8-10	xx (%)	xx (%)	xx (%)

[1] 0=None to 10=Worse.

Investigator evaluation of Injection Site Reactions

The injection site reactions are reported as part of the TEAEs. For each subject with an injection site reaction, subject profiles will be produced that summarize corresponding adverse event data along with demographic variables, dose of study drug, duration of exposure, drug discontinuation, CRP and eosinophil levels and medications used to treat the injection site reaction

10 CHANGES IN SAP COMPARED TO STUDY PROTOCOL

10.1 Addition of Exploratory Outcome Measures

After finalization of the protocol, following outcome measures were added to the list of exploratory outcome measurements.

Efficacy outcome parameters by a CCR5 Haplotype biomarker :

- Change from baseline in hepatic fat fraction assessed by magnetic resonance imaging-derived proton density fat fraction (MRI-PDFF) at week 14 by CCR5 Haplotype biomarker
- Change from baseline in fibro-inflammatory activity as assessed by cT1 (corrected T1) assessed by multiparametric magnetic resonance imaging (MRI) of liver at week 14 by CCR5 Haplotype biomarker

Efficacy outcome parameters by a CCR5 calcium flux biomarker :

- Change from baseline in hepatic fat fraction assessed by magnetic resonance imaging-derived proton density fat fraction (MRI-PDFF) at week 14 by CCR5 calcium flux biomarker
- Change from baseline in fibro-inflammatory activity as assessed by cT1 (corrected T1) assessed by multiparametric magnetic resonance imaging (MRI) of liver at week 14 by CCR5 calcium flux biomarker

11 DATA HANDLING AND RECORD KEEPING

11.1 Recording and Collection of Data

The primary source document for this study will be the subject's medical record. If separate research records are maintained by the Investigator(s), the medical record and the research records will be considered the source documents for the purposes of auditing the study.

Applicable source data will be manually transcribed to approve case report forms (CRF). The Investigator is ultimately responsible for the accuracy of the data transcribed on the forms. All source documents and CRFs will be completed as soon as possible after the subject's visit.

The Investigator will review the CRFs to indicate that, to his/her knowledge, they are complete and accurate. Designated source documents will be signed and dated by the appropriate study personnel. The Investigator must agree to complete and maintain source documents and CRFs for each subject participating in the study.

All research data will be entered, either electronically or manually, into a computerized database. The clinical database will be designed by the clinical data manager in accordance with 21 CFR Part 11 and based on protocol requirements defined by the Sponsor in association with the Lead Investigator.

The Investigator will maintain a confidential list of study subjects that will include each subject’s study number, name, date of birth, and unique hospital identification number if applicable. This list will be kept by the Investigator and will not be collected by the Sponsor. A notation will be made in the subject’s case history/medical chart that he/she is participating in a clinical study and has provided a signed and dated ICF as well as a release for protected health information as required by local policies. The Investigator must also maintain a separate screening log of all the subjects screened for participation in the study; it should include gender, age, eligibility status, reason for ineligibility, if applicable; and study allocated subject number, if applicable.

11.2 Clinical Data Management

The Sponsor and/or designated CRO will be responsible for the processing and quality control of the data. Data management will be carried out as described in the Sponsor’s or CRO’s standard operating procedures (SOPs) for clinical studies.

The handling of data, including data quality control, will comply with regulatory guidelines (e.g., ICH E6 GCP, and local regulations where applicable) and the Sponsor’s or the CRO’s SOPs as well as provisions of the study-specific Data Management Plan.

11.3 Data Transfer to Sponsor

All data formatted to meet the SDTM (Study Data Tabulation Model) standard of Clinical Data Interchange Standards Consortium (CDISC) along with a Define.doc file that lists attributes of data variables will be transferred to the sponsor.

12 REFERENCES

- ASA. Ethical Guidelines for Statistical Practice. Prepared by the Committee on Professional Ethics, April, 2016.
- The Royal Statistical Society: Code of Conduct (2014).
- E8 General Considerations for Clinical Trials, ICH Guidance, Federal Register, 1997.
- E9 Statistical Principles for Clinical Trials, ICH Guideline, Federal Register, 1998
- E9 (R1) Statistical Principles for Clinical Trials, ICH Guideline, Federal Register, 1998

- Guideline for the Format and Content of the Clinical and Statistical Section of an Application, 2017.
- Guideline for Industry: Structure and Content of Clinical Study Reports (ICH E3), July 1996.